
Discovery and Mechanism of SARS-CoV-2 Main Protease Inhibitors.

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Funding Grants: Development of COVID-19 Antiviral Therapy Using Human iPSC-Derived Lung Organoids

Public Summary:

The emergence of a new coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), presents an urgent public health crisis. Without available targeted therapies, treatment options remain limited for COVID-19 patients. Using medicinal chemistry and rational drug design strategies, we identify a 2-phenyl-1,2-benzoselenazol-3-one class of compounds targeting the SARS-CoV-2 main protease (M(pro)). FRET-based screening against recombinant SARS-CoV-2 M(pro) identified six compounds that inhibit proteolysis with nanomolar IC₅₀ values. Preincubation dilution experiments and molecular docking determined that the inhibition of SARS-CoV-2 M(pro) can occur by either covalent or noncovalent mechanisms, and lead E04 was determined to inhibit M(pro) competitively. Lead E24 inhibited viral replication with a nanomolar EC₅₀ value (844 nM) in SARS-CoV-2-infected Vero E6 cells and was further confirmed to impair SARS-CoV-2 replication in human lung epithelial cells and human-induced pluripotent stem cell-derived 3D lung organoids. Altogether, these studies provide a structural framework and mechanism of M(pro) inhibition that should facilitate the design of future COVID-19 treatments

Scientific Abstract:

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